REMARKS

By this amendment claim 1 is amended; claims 1-8 are pending. Support for the amendment is discussed below. No issue of new matter arises. Entry of the amendment and reconsideration and withdrawal of all pending rejections in each of the multiple parts thereof are respectfully requested.

Rejections Under 35 USC §101

Claims 1-5 were rejected under 35 USC §101 as allegedly being directed to non-statutory subject matter. While not agreeing with the legal basis of this rejection, Applicants amend claim 1 as suggested by the Examiner to recite "non-human animal". Applicants further note that the specification at page 3, lines 16-18 specifies that a transgenic animal is "understood to mean any nonhuman animal . . . ." Thus no issue of new matter arises. This amendment obviates the rejection of claim 1 and claims dependent therefrom. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-8 were rejected under 35 USC §101 as allegedly lacking patentable utility. Applicants respectfully traverse this rejection. The Office Action characterizes the claimed subject matter as "transgenic animals wherein the transgenic animal expresses a multimutated form of presenilin 1 and wherein the transgenic animal exhibits an apoptotic phenotype in its renewable peripheral tissue." The Office Action further elucidates the rejection stating:

> While the specification teaches these embodiments of the claimed mice, nothing in the specification or the art teaches that there is a relationship between PS1, T-lymphocytes, apoptosis, and Alzheimer's disease. In other words, the claimed animals would be used in a study to further determine the relationship between PS1, T lymphocytes, apoptosis, and Alzheimer's disease.

The Office Action acknowledges that the specification teaches that exemplary mice of the claimed invention exhibit higher levels of apoptosis in T-lymphocytes. These mice are therefore useful at least at this level, e.g., as a model to monitor apoptosis. Only a single substantial and specific utility is required to overcome the statutory hurdle. An invention is not required to meet every utility conceivable. This single substantial utility is sufficient to render compliance with 35 U.S.C. §101. Reconsideration and withdrawal of this rejection are respectfully requested.

As further evidence of utility Applicants refer to the specification, page 6, paragraph 2, which summarizes the examples as demonstrating that animals of the instant invention develop

cellular impairments found in AD and exhibit increased sensitivity to apoptosis such as found in AD. Thus the apoptotic phenomena allow monitoring of status, e.g., efficacy of treatment regimens, without sacrifice of the animal. At page 7, second paragraph a further utility is provided in the teaching that Ca^{++} and free radical metabolism in the animals of the present invention are similar to those observed with AD patients. At page 7, penultimate paragraph, the specification teaches a utility of detecting compounds particularly suitable for the treatment of AD. The examples as shown in the figures demonstrate that AD associated characteristics, such as increased apoptosis, free radical production and altered calcium transport, of the multimutated transgenic animals of the instant invention can be monitored using peripheral samples thereby allowing minimally invasive monitoring without sacrificing the animal. See e.g., at page 29, paragraph 2, the specification discusses free radical metabolism deficiencies also being present in AD patients. The relevance of the present animal model to minimally invasive monitoring of AD associated characteristics is thus confirmed. Although all these utilities are not necessary to demonstrate utility required by 35 USC §101, the collection of demonstrated utilities, substantial and specific, clearly exceeds the requirements of the statute. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections Under 35 U.S.C. §112

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. This rejection is constructed in many aspects or parts. To provide a complete response each of the recognized parts are addressed in turn below.

The Office Action acknowledges that the specification teaches several embodiments, but alleges lack of enablement based on the false allegation that nothing in the art or specification teaches a relationship between apoptosis and PS1, i.e., that no guidance is provided that certain mutations or amino acid combinations are associated with apoptosis. The Office Action states that the artisan would "need to establish a relationship between PS1 and apoptosis before the claimed transgenic animal or a cell obtained from the claimed transgenic animal can be used in a method for screening for compounds." Applicants respectfully traverse this rejection.

Applicants respectfully refer to the present specification, e.g., Example 2, wherein is demonstrated that the cells of transgenic mice of the example show increased apoptosis

compared to non-transgenic littermates as well as from mice with wild type PS1. The needed relationship between PS1 and apoptosis as mandated by the Examiner is hereby established in the instant specification. Reconsideration and withdrawal of this rejection are respectfully requested.

Another aspect of the present rejection relates to promoters. The Office Action mentions that not all promoters are functional across multiple species. See Office Action, pages, 7-10. This is an argument without merit. The Office Action itself demonstrates the knowledge in the art of the availability of different promoters and that not all are ubiquitous in effect. Thus the skilled artisan is aware of promoters, selection bases and uses. The present exemplary promoter (not recited as necessary in the claims) is characterized as a ubiquitous promoter. While Applicants concede that not all promoters are universally effective in all species, the claims specifically recite a transgenic animal expressing the mutated protein. The scope is thus limited to those embodiments in which the protein can be functionally expressed, e.g., those with functional promoters associated therewith. The skilled artisan is quite capable of selecting a suitable promoter for a particular expression system without undue experimentation. Thus in this respect the present invention does not suffer from lack of enablement. The Office Action only speculates and provides no demonstrable "reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." See MPEP 2164.04. It is well within the skill in the art and is clearly not undue experimentation to select a promoter functional in a given species. Reconsideration and withdrawal of this rejection are respectfully requested.

A further aspect of this rejection relates to variation in insertion site of a transgene. Applicants acknowledge that interruption of a gene by insertion of genetic material therein may inactivate the interrupted gene and result in a particular phenotypic expression of the cell or progeny thereof. However, the chance that in some embodiments an additional phenotypic pattern may obtain does not detract from the fact that the transgene described in the present invention has its own demonstrated phenotypic pattern. In general, the inserted gene (e.g., transgene) has an associated phenotype when expressed that is distinguishable from the wild type animal. That is the reason the gene was inserted! Although there may be other genes expressed (which there will be in a living animal) variability of expression of the thousands of other genes does not eliminate expression of a phenotype associated with the inserted gene, e.g., in the instant transgenic animal and cells obtained therefrom. Thus the present invention is enabled

even though in some embodiments or trials, an additional effect may be observed relating to a specific site of insertion. Furthermore the claims do not recite "predicting phenotypes for all transgenic animals . . .." Page 10, lines 16-19. Thus the allegation that such prediction is not enabled is not a proper basis for rejection in this application. Reconsideration and withdrawal of this rejection are respectfully requested.

In another aspect of this rejection, at page 11, the Office Action focuses on renewable tissue. Once again the Office Action provides only speculation, not objective evidence or "reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." See, e.g., MPEP 2164.04. The Office Action merely speculates that despite the examples that demonstrate working the present invention some tissues may not be as easily used in practice. This is mere speculation. But even if true does not disenable the present invention. While the instant specification does not provide an example relating to every tissue and cell type that can be found in an organism, a working example is provided. The Office Action provides no evidence that any other tissue would not similarly work or that the skilled artisan would require undue experimentation to practice the claimed invention. The skilled artisan would clearly understand that monitoring apoptosis in a red blood cell would be futile. This fact does not disenable the present invention as no undue experimentation can be said to be required. While peripheral blood which contains white blood cells is a great example because of ease in obtaining tissue samples, other tissues, though more difficult to obtain and possibly requiring more invasive procedures, might be desirable as sentinels in other circumstances. Additionally, the Office Action does not provide any evidence to support the postulated necessity of determining common features necessary between peripheral tissues such that expression of multimutated PS1 would result in apoptosis. The present invention is enabled without such additional background information. The skilled artisan is well aware that a viable cell is a necessary requisite for apoptosis, therefore a myriad of cell organelles and structures including a nucleus must be in common. There is no requirement in patent law that a specification teach what is known. In fact, "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." MPEP2164.05a. The specification likewise is not required to teach more than is known so long as requirements of the patent laws are met. Thus this aspect of the rejection appears improper. Reconsideration and withdrawal of this rejection are respectfully requested.

In yet another aspect of this rejection, in a portion spanning pages 12 and 13, a theory is posited that the skilled artisan would need to know what portions of SP1 were involved in the apoptotic pathway. Applicants respectfully assert that such guidance in unnecessary. Although the present specification teaches multiple mutations that increase apoptosis, no undue experimentation is required on the part of the skilled artisan to use random or directed mutagenesis to make additional or different mutations with apoptotic effect. The Office Action provides absolutely no evidence of a requirement for particularity of mutations in PS1 that effect or augment apoptosis. The skilled artisan is freely capable without undue experimentation to select and construct a number or specific combination of mutations that work in the particular chosen model. The skilled artisan routinely constructs mutated genes and inserts such genes into cells (including progeny cells). Such work is routine, not undue. The Examiner is directed to PubMed by way of example where a search on "mutagenesis" (January 11, 2006) provided 165,308 hits. Clearly use of such tool is routine rather than undue.

In still another aspect of this rejection, the paragraph bridging pages 13 and 14 mentions claims 1-5 and neurodegenerative diseases. Claims 6 and 8 are the only claims that recite neurodegenerative diseases. The paragraph mentions "neurodegenerative diseases such as Parkinson's, Tay Sachs, and Lou Gehrig's diseases." The Office Action acknowledges that the specification in fact does teach a relationship between Parkinson's and PS1. Then, in an apparent misunderstanding of the invention, the Office Action states, "an artisan does not know what symptoms of Alzheimer's disease one should monitor when screening for compounds which are used to treat Alzheimer's disease". This misses the whole point. The present invention provides a means of using a peripheral tissue or a cell as a surrogate for complex analysis of Alzheimer's symptoms. For example, as taught in the instant specification, apoptosis, Ca^{++} metabolism, or oxidative pathways might be monitored. The present invention thereby provides a screen and monitoring capability for compounds intended for treatment of neurodegenerative disorders. While the identified compounds may initially be intended for treatment of neurodegenerative disease, not all identified compounds will necessarily be used to treat humans. Some compounds likewise may be useful for treating, e.g., other degenerative diseases. Later stages in drug development might be expected to involve further monitoring, such as neuronal tissue analysis or possibly behavioral traits. These would be separate events in a pathway to market that includes many discreet parts. Contrary to the impression the Office

Action suggests, the present invention does not claim a complete tool for bringing a drug to market. The present invention provides a valuable tool of the many necessary to complete the entire path. In view of the apparent misconstruction of the claims to require symptomatic analysis, Applicants respectfully request reconsideration and withdrawal of this aspect of the rejection.

In an apparently separate rejection commencing on page 14, claims 1-8 were rejected 35 U.S.C. §112, first paragraph, as allegedly lacking written description in that the Office Action alleges that the inventors did not posses the invention. Applicants respectfully traverse this rejection. The Office Action asserts that the specification "does not teach how to make any multimutant PS1, such that the mutant PS1 has a role in increasing apoptosis in peripheral tissue." The specification in fact does teach that the PS1 gene is associated with apoptosis. It is well known in the art how to find, isolate and mutate analogous and homologous genes. The present inventors have conceived their invention and demonstrated with examples actual working of the invention. Possession is clearly established. The rejection in asserting that the specification "does not indicate how" seems to cross out of the written description realm. This language appears to be more appropriate as an enablement issue. Enablement issues were addressed above and need not and should not be reconsidered here in the context of written description. In this rejection, the Office Action further propounds: "The skilled artisan cannot envision all the possible variant amino acid sequences which would result in a multimutant PS1 protein with increased apoptotic activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods used." (Emphasis in original text.) Plainly stated this is not a valid rejection under US law. The issue of written description set forth in this rejection was whether the inventors possessed the claimed invention. What the skilled artisan envisions has no place in this type rejection. Furthermore, nowhere in the patent statutes is there a requirement that every possible embodiment of an invention be demonstrated or envisioned. Quite the contrary is established law. E.g., Wands stands for the principle that species patents may issue after a genus patent. If envisioning every possible embodiment were the case every improvement patent would invalidate its predecessor. Clearly this is not law. For example, any patent practitioner knows that every patent Examiner who has issued such species or improvement patent is not commenting on the invalidity of previous patents. See, e.g., MPEP 1701: **Office Personnel Not To Express Opinion on**

Validity*>,< Patentability>, or Enforceability< of Patent. Thus the Patent Office acknowledges that issuance of an improvement patent is not a comment on validity of a predecessor. Similarly "comprising" transition words would not be allowable because the open-endedness did not envision every conceivable embodiment. Accordingly, it is well-established law that every embodiment need not be envisioned in a valid patent. The statement that "one cannot envision what one has not conceived" is therefore not applicable in this context. Reconsideration and withdrawal of this rejection are respectfully requested.

In the portion of the Office Action bridging pages 17 and 18, claim 4 was rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. Applicants respectfully traverse this rejection. Claim 4 recites as its penultimate word "and/or". Clearly, since claim 5 depends from claim 4, the "or" (the same as the "and") must apply across the entire list, not just to the ultimate member of the group. If the Examiner still believes that this claim is unclear, Applicants offer to amend the claim as a Markush type claim. Please advise. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

The foregoing is submitted as a full and complete response to the Action mailed on July 14, 2005, and the allowance of all claims is respectfully requested. If there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited to call the undersigned attorney at (908) 231-3776.

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. 18-1982.

Respectfully submitted,

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